Genome-wide association study implicates immune dysfunction in the development of Hodgkin lymphoma

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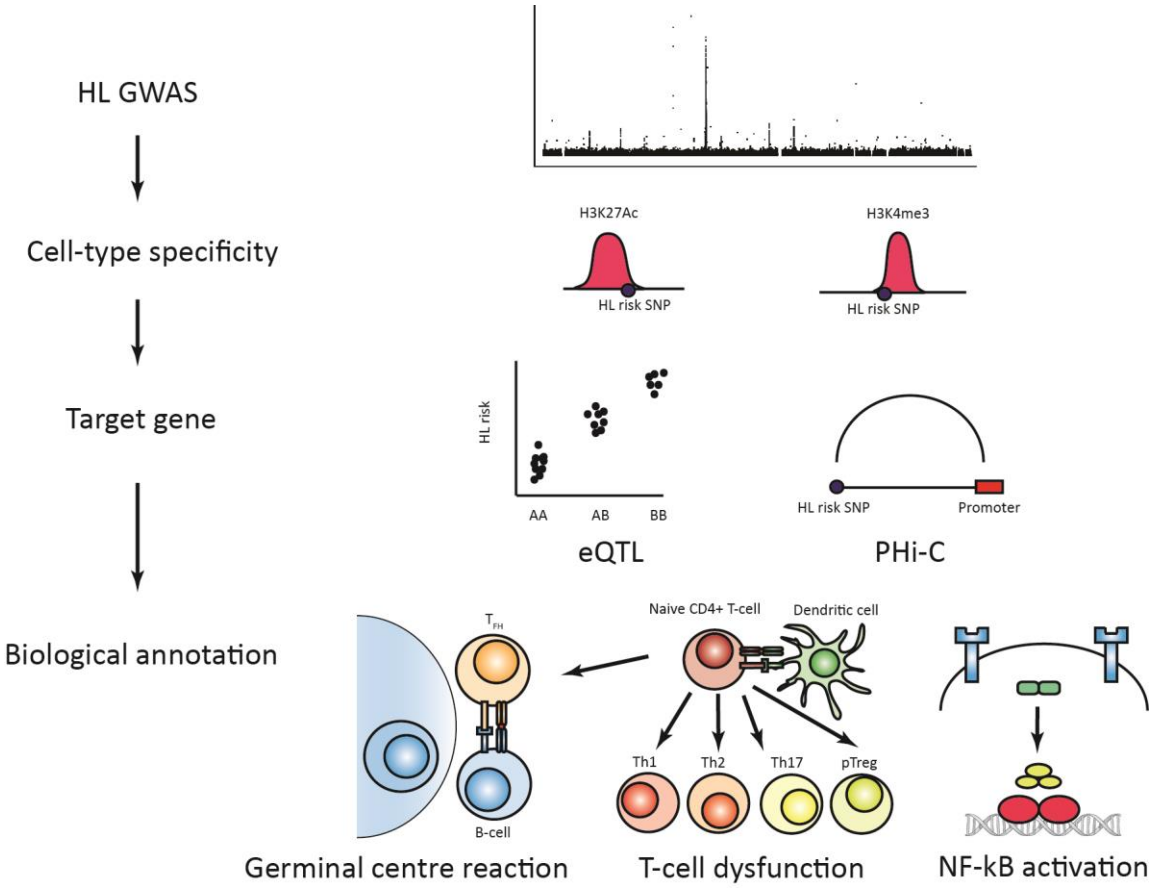
VISUAL ABSTRACT



KEY POINTS:

- Variation at 6p21.31, 6q23.3, 11q23.1, 16p11.2 and 20q13.12 influences risk of HL
- Genetic predisposition implicates germinal centre dysfunction, disrupted T-cell function, and NF-κB activation in the pathogenesis of HL

ABSTRACT

To further our understanding of inherited susceptibility to Hodgkin lymphoma (HL), we performed a meta-analysis of seven genome-wide association studies totalling 5,325 HL cases and 22,423 controls. We identify five new HL risk loci at 6p21.31 (rs649775, $P = 2.11 \times 10^{-10}$), 6q23.3 (rs1002658, $P = 2.97 \times 10^{-8}$), 11q23.1 (rs7111520, $P = 1.44 \times 10^{-11}$), 16p11.2 (rs6565176, $P = 4.00 \times 10^{-8}$) and 20q13.12 (rs2425752, $P = 2.01 \times 10^{-8}$). Integration of gene expression, histone modification and *in situ* promoter capture Hi-C data at the five new and 13 known risk loci implicates dysfunction of the germinal centre reaction, disrupted T-cell differentiation and function, and constitutive NF-κB activation as mechanisms of predisposition. These data provide further insights into the genetic susceptibility and biology of HL.

INTRODUCTION

Hodgkin lymphoma (HL) comprises classical Hodgkin lymphoma (cHL) (~95% of cases) and nodular lymphocyte predominant HL (NLPHL, ~5% of cases)[1]. While cHL and NLPHL are defined by the Hodgkin and Reed-Sternberg (HRS) cell and the lymphocyte predominant (LP) cell respectively, both diseases are thought to arise from the malignant transformation germinal centre (GC) B-cell[2,3]. Furthermore, both cHL and NLPHL demonstrate a paucity of these neoplastic B-cells within a background of reactive inflammatory cells that includes large populations of CD4+ T-cells[4,5].

A viral or infectious agent has long been considered a major etiological factor for HL, with Epstein-Barr virus (EBV) being the posited infectious agent[6,7]. However, the EBV genome is only identifiable in a minority of HL cases and epidemiological data supports a causal role for the virus in EBV-positive HL only[8]. Evidence for genetic susceptibility to HL is provided by the elevated familial risk as well as the high concordance between monozygotic twins[9-11]. More recently, genome-wide association studies (GWAS) have confirmed an HLA association for HL and have identified single nucleotide polymorphisms (SNPs) at 13 non-HLA loci influencing risk[12,13].

To gain further insight into HL susceptibility, we have conducted a meta-analysis of data from seven independent GWAS and report five new HL risk loci[12-14]. Integration of gene expression, histone modification and *in situ* promoter capture Hi-C data (PCHi-C) at the five new and the 13 known risk loci provides evidence for cell-type specificity in B- and T-cells and implicates dysfunction of the germinal centre reaction, disrupted T-cell differentiation and function, and constitutive NF-κB activation as mechanisms by which loci influence HL risk.

MATERIALS AND METHODS

Ethics

Collection of patient samples and associated clinico-pathological information was undertaken with written informed consent. Relevant ethical review boards approved the individual studies in accordance with the tenets of the Declaration of Helsinki (UK-GWAS MREC 03/1/096, German-GWAS University of Heidelberg 104/2004 and UK-GWAS-NSHLG MREC 09/MRE00/72). The diagnosis of HL in all cases was established in accordance with World Health Organisation guidelines.

Genome-wide association studies

We used GWAS data generated on three non-overlapping case–control series of Northern European ancestry, which have been the subject of previous analyses (**Supplementary Tables 1** and **2**)[12]. The UK-GWAS was based on 622 cases ascertained through the Royal Marsden Hospital National Health Service Trust Family History study during 2004–2008[15], and 5,677 controls from the UK Wellcome Trust Case Control Consortium 2 (WTCCC2)[16]. The German-GWAS comprised 1,001 cases ascertained by the German Hodgkin Study Group during 1998–2007, and 2,092 controls from the Heinz Nixdorf Recall (HNR) study[17]. The UK-NSHLG-GWAS utilised 1,717 cases ascertained through the NSHLG (http://www.public.ukcrn.org.uk) from 2010 to 2013[12]. Controls comprised: (1) 2,976 cancer-free men recruited by the PRACTICAL Consortium—the UK Genetic Prostate Cancer Study (UKGPCS) (age < 65 years), a study conducted through the Royal Marsden NHS Foundation Trust and SEARCH (Study of Epidemiology & Risk Factors in Cancer), recruited via GP practices in East Anglia (2003–2009), (2) 4,446 cancer-free women from across the UK via the Breast Cancer Association Consortium (BCAC). Details of the genotyping platform and quality control measures applied to each of the three GWAS have been described previously and are detailed in **Supplementary Tables 3** and **4**[12,15,18,19]. Briefly, individuals with a low call rate (< 95%) as well as all individuals evaluated to be of non-European ancestry, were excluded (**Supplementary Figure 1**). Eigenvectors for the GWAS data sets were inferred using smartpca (part of EIGENSOFT) by merging cases and controls with Phase III HapMap samples[20]. For apparent first-degree relative pairs, we excluded the control from a case–control pair or the individual with the lower call rate (**Supplementary Table 3**). SNPs with a call rate < 95% were excluded as were those with a MAF < 0.01 or displaying deviation from Hardy–Weinberg equilibrium (HWE) (*i.e.*, $P < 10^{-6}$, **Supplementary Table 4**). GWAS data were phased with SHAPEIT3[21], and imputed to >10 million SNP using IMPUTE4 v1.0[22] and a merged reference panel consisting of data from 1000 Genomes Project (phase 3)[23] and UK10K (EGAD00001000776)[24]. Imputation was

conducted separately for each study from set of SNPs common to cases and controls. Poorly imputed SNPs (defined by an information measure < 0.80) were excluded. Tests of association between SNPs and HL were performed using logistic regression under an additive genetic model in SNPTESTv2.5.2[25]. The adequacy of the case–control matching was evaluated using Q–Q plots of test statistics (Supplementary Fig. 2). The inflation factor λ_{1000} was based on the 90% least-significant SNP scaled to 1000 cases and 1000 controls.

In addition to analysing data from these three GWAS, we made use of pre-processed association test statistics for HL risk from a meta-analysis of three additional GWAS (USC-IARC-UC-GWAS) comprising 1,816 HL cases and 7, 879 contols[13,26,27], and an analysis of 432 HL cases and 337,208 unaffected individuals[14] from the UK Biobank accessed through the Global Biobank Engine.

Meta-analysis

Meta-analyses were performed under a fixed-effects model using META v1.7[25]. Cochran's Q-statistic to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation due to heterogeneity were calculated; an I^2 value $\geq 75\%$ is considered to be characteristic of large heterogeneity[28]. Where the same controls were used in both the UK-GWAS and the USC-IARC-UC GWAS, these controls were excluded from the UK-GWAS association analysis.

Cell culture

L-428 HL cells were obtained from DSMZ and were cultured at 37°C in RPMI 1640 supplemented with 10% heat inactivated FBS (Thermo Scientific). Cell line identity was confirmed by STR-profiling. Cells were regularly tested for mycoplasma contamination (PromoCell, PK-CA91).

ChIP-seq analysis

L-428: ChIP-seq was performed on H3K27Ac and H3K4me3, for using antibodies obtained from Diagenode. Briefly, after cell lysing, sonication of nuclei was performed 293 (UCD-300, BioRuptor) to obtain 150-500bp fragments. ChIP reaction was performed on a Diagenode SX-8G IP-Star Compact using Diagenode automated Ideal Kit reagents (C01010011). Protein A beads were incubated for 10 hours with 3-6µg of antibody and 2-4 million of sonicated cell lysate. ChIP samples were de-crosslinked at 65°C for 4 hours and subsequently treated for 30 minutes with RNAse Cocktail and proteinase K. DNA was then purified (MiniElute PCR purification kit, Qiagen), followed by library preparation according to manufacture (HTP Illumina library preparation kit, KAPA Biosystems). Fourteen cycles of PCR were performed, followed by size selection for 200-400bp fragments and final library purification (GeneRead Size Selection kit, 301 Qiagen). ChIP libraries were sequenced

using HiSeq 2000 (Illumina) with 100bp single-ended reads. Generated raw reads were filtered for quality (Phred33 ≥ 30) and length (n ≥ 32), and adapter sequences were removed using Trimmomatic v0.2235. Reads passing filters were then aligned to the human reference (hg19) using BWA v0.6.1. Peak calls are obtained using MACS2 v 2.0.1.

Histone modification data from primary blood cells: H3K27Ac and H3K4me3 data from >100 samples from >30 cell types from the Blueprint Epigenome Consortium were analysed[29].

Cell-specificity analysis

Overlap enrichment analysis of HL risk SNPs with H3K4me3 and H3K27Ac peaks was performed as described by Trynka *et al*[30]. Briefly, we evaluated whether the HL risk SNPs and SNPs in LD ($r^2 > 0.8$) with the sentinel SNP, were enriched at H3K4me3 and H3K27Ac ChIP-seq peaks, in blood cells and the HRS cell line L-428 by a permutation procedure with 10^5 iterations.

Promoter capture Hi-C

In situ Hi-C libraries for **L-428** were prepared as previously described[31,32]. Briefly, 25 million cells were fixed in 1% formaldehyde for 10 min. Cross-linked DNA was digested with HindIII (NEB, R0104) and chromatin ends were filled and marked with biotin-14-dATP (ThermoFisher, 19524-016). The resulting blunted ended fragments were ligated at 16°C in the nucleus with T4 DNA ligase (NEB, M0202) to minimise random ligation. DNA purified after crosslinking was reversed by proteinase K (Ambion, AM2546) treatment. DNA was sheared by sonication (Covaris, M220) and 200-650bp fragments selected. Biotin tag DNA was pulled down with streptavidin beads and ligated with Illumina paired end adapters (Illumina). Six cycles of PCR were performed to amplify libraries before capture. Promoter capture was based on 32,313 biotinylated 120-mer RNA baits (Agilent Technologies) targeting both ends of HindIII restriction fragments that overlap Ensembl promoters of protein-coding, non-coding, antisense, snRNA, miRNA and snoRNA transcripts (**Supplementary Data**). After library enrichment, a post-capture PCR amplification step was carried out using 6 amplification cycles. Hi-C and PCHi-C libraries were sequenced using HiSeq 2000 technology (Illumina). Reads were aligned to the GRCh37 build using Bowtie2 v2.2.6[33] and identification of valid di-tags was performed using HiCUP v0.5.9[34]. To declare significant contacts, HiCUP output was processed using CHiCAGO v1.1.8[35]. Data from three independent biological replicates were combined to define definitive set of contacts. Publicly accessible PCHi-C data generated in B- and T-cell populations were downloaded from the Open Science Framework[36].

Chromatin interactions relevant to HL risk loci were defined as contacts overlapping with HL risk SNPs and SNPs in LD (r^2 >0.8 with the sentinel SNP), with promoters within a 2Mb window of the

sentinel SNP, and with a score ≥ 5.0[35]. Plotting of HL association data and chromatin contacts was performed using visPIG[37].

Expression quantitative trait loci analysis

An analysis of associations between the SNPs (r^2 > 0.8) at each locus and tissue-specific changes in gene expression was performed using summary statistics from three publicly available resources: (i) lymphobastoid cell line (LCL) expression from the MuTHER (n = 825) consortium[38]; (ii) LCL expression from the GTEx consortium (n = 114)[39]; (iii) CD4+ and CD8+ T-cells from 313 individuals[40]. Statistical significance was assigned after correcting for the number of probes at each locus (microarray) or the number of transcripts at each locus (RNA-seq) for each expression dataset.

Genetic correlation with infection

To estimate the genetic correlation between specific infections and all HL, and NSHL and MCHL subtypes[41], we used LD score regression. Summary statistics for self-reported infectious diseases from over 200,000 participants in 23andMe included[42]: chickenpox, shingles, cold sores, mononucleosis, mumps, hepatitis B, plantar warts, positive tuberculosis test results, streptococcus throat infection, scarlet fever, pneumonia, bacterial meningitis, yeast infections, urinary tract infections, tonsillectomy, childhood ear infections, myringotomy, measles, hepatitis A, rheumatic fever, common colds, rubella, and chronic sinus infection.

Mendelian randomisation

We performed two-sample MR using SNPs associated with specific infection-related traits as IVs. SNPs associated with each of the infection-related traits at genome-wide significance (i.e. $P \leq 5.0 \times 10^{-8}$) were used as IVs[42]. We analysed infection-related traits for which >2 SNPs had been shown to be associated with the specific infection (tonsillectomy, mumps infection, childhood ear infection and yeast infections). To avoid co-linearity between SNPs for each trait, we excluded SNPs that were correlated (i.e. r^2 value of ≥ 0.01) within each trait, and only considered the SNPs with the strongest effect on the trait for use as IVs. Where data on an IV was not present in the outcome trait, a proxy was utilised (r^2>0.6). Details of the IVs used are detailed in **Supplementary Data.** For each SNP, we recovered the chromosome position, risk allele, association estimates (per-allele log-OR) and standard errors. The allele that was associated with increased risk of the exposure was considered the effect allele. The odds ratios (OR) of HL, NSHL and MCHL per unit of standard deviation increment for each infection-related trait, were estimated using the 'Mendelian randomisation' R package[43]. Given that traits analysed are binary outcomes, the maximum likelihood method was

employed with the resulting causal effect estimate representing the odds for HL risk per unit increase in the log OR for infection-related trait.

RESULTS

Association analysis

We analysed summary level GWAS data generated on HL cases and controls of European ancestry[12] from three sources (**Supplementary Tables 1-4**): (1) two GWAS of UK cases and controls and one GWAS of German cases and controls, totalling 3,077 cases and 14,546 controls (Discovery GWAS)[12]; (2) the Stanford Global Biobank Engine, an analysis of 432 HL cases from the UK Biobank[14] and (3) a meta-analysis of three published HL GWAS totalling 1,816 HL cases and 7,879 controls (USC-IARC-UC-GWAS)[13,26,27].

In a meta-analysis of data from the seven studies, we identified new genome-wide significant associations for HL (**Figure 1** and **Table 1**), at 6p21.31 (rs649775, $P = 2.11 \times 10^{-10}$, marking *ITPR3-UQCC2-IP6K3*), 6q23.3 (rs1002658, $P = 2.97 \times 10^{-8}$, marking *OLIG3-TNFAIP3*), 11q23.1 (rs7111520, $P = 1.44 \times 10^{-11}$, marking *POU2AF1*), 16p11.2 (rs6565176, $P = 4.00 \times 10^{-8}$, marking *MAPK3-CORO1A*) and 20q13.13 (rs2425752, $P = 2.01 \times 10^{-8}$, marking *NCOA5-CD40*). In addition, we identified a promising association at 1p13.2 (rs2476601, $P = 4.20 \times 10^{-7}$, marking *PTPN22*).

The bimodal incidence of HL and the higher rate of nodular sclerosis Hodgkin lymphoma (NSHL) and EBV-negative HL in young adults suggest differences in the etiology of HL subtypes[8]. Case-only analysis however provided no evidence for an age or histological subtype association for the five new risk SNPs. (**Supplementary Tables 5 and 6**).

Cell specificity of associations

Trynka *et al.*, have recently shown that chromatin marks highlighting regulatory regions, overlap with phenotype-associated variants in a cell-type specific manner[30]. To examine for cell-type specificity of the five new and 13 known HL risk loci we analysed H3K4me3 and H3K27Ac chromatin marks which annotate regulatory regions, in over 125 samples from 38 hematopoietic cell types from BLUEPRINT[29,30] and the HRS cell line L-428. The H3K27Ac histone mark is predominantly associated with enhancers and of all the histone marks demonstrates the greatest enrichment of promoter interacting regions[36]. The H3K4me3 histone mark is predominantly associated with promoters and transcribed regions, and has previously been shown to be the most phenotypically cell-type specific[30,44]. Cell types showing the strongest enrichment of risk SNPs at H3K4me3 marks were CD4+ T-cells from venous blood ($P = 2.9 \times 10^{-3}$), CD3- CD4+ CD8+ positive thymocytes ($P = 5.7 \times$

10^{-3}) and tonsillar derived germinal centre B-cell ($P = 6.3 \times 10^{-3}$) (**Supplementary Table 7**). Cell types with the strongest enrichment of risk SNPs at H3K27Ac marks were CD8+ T-cells from venous blood ($P = 3.0 \times 10^{-4}$), CD3+ CD4+ CD8+ thymocytes ($P = 5.6 \times 10^{-4}$), CD4+ thymocytes ($P = 2.7 \times 10^{-3}$) and L-428 ($P = 7.9 \times 10^{-3}$) (**Supplementary Table 8**). Based on the co-localisation of variants with active chromatin marks, we calculated an enrichment scores for each genetic association (**Figure 2**)[30]. High SNP regulatory scores were also shown in T-cells cells at 3p24.1, 6q22.33, 6q23.3 and 10p14 risk loci, in B-cells at 2p16.1, 3q28, 8q24.21, 11q23.1 and 20q13.12 risk loci and in HRS cells at 3p24.1, 5q31.1, 6q22.33, 6q23.3, 10p14, 13q34 16p13.13 and 20q13.12.

Identification of candidate target genes at HL risk loci

Most GWAS loci map to non-coding regions of the genome and influence gene regulation[45]. Hence, to gain insight into the biological mechanisms for the associations at the 5 new and 13 known HL risk loci, we first performed expression quantitative trait locus (eQTL) analysis on expression data in B-cell lymphoblastoid cell lines (LCL) and in CD4+ and CD8+ T-cells. We identified eQTLs in LCL at 6p21.31 (*ITPR3*), 6q23.3 (*AHI1*, *ALDH8A1*), 10p14 (*GATA3*), 11q23.1 (*COLCA1*, *COLCA2*), 13q34 (*UPF3A*, *CDC16*), 16p13.13 (*SOCS1*), 16p11.2 (*MAPK3*, *BOLA2*) and 20q13.12 (*CD40*, *WFDC10B*); in CD4+ T-cells at 6q23.3 (*AHI1*) and 13q34 (*CDC16*); and in CD8+ T-cell at 3p24.1 (*EOMES*), 6q23.3 (*AHI1*) and 13q34 (*CDC16*) (**Table 2** and **Supplementary Tables 9** and **10**).

Chromatin looping interactions between enhancer elements and promotors are central to regulation of gene expression[46]. To link risk loci to candidate target genes we analysed PCHi-C data. Firstly, we examined physical interactions at genomic regions annotated by HL risk loci (including variants with an $r^2 > 0.8$) using publicly accessible PCHi-C in naïve and total B-cells, as well as CD4+ and CD8+ T-cells[36]. Secondly, we generated and analysed PCHi-C data for the HRS cell line L-428. We observed concordance between H3K27Ac peaks and chromatin contacts in B-, T- and HRS cells for specific HL risk loci. Notable chromatin contacts were found in the B-lineage at 2p16.1 (*REL*), 6p21.31 (*BAK1*), 8q24.21 (*MYC*, *PVT1*), 13q34 (*RASA3*), 16p.13.13 (*RMI2*) and 20q13.12 (*CD40*); in the T-lineage at 3p24.1 (*EOMES*, *AZI2*), 6p21.31 (*BAK1*), 6q22.33 (*THEMIS*, *PTPRK*), 6q23.3 (*MYB*), 13q34 (*RASA3*) and 16p13.13 (*SOCS1*, *RMI2*); and in L-428 at 3p24.1 (*AZI2*, *CMC1)*, 6q23.3 (*MYB*), 6q23.3 (*TNFAIP3*) and 16p13.13 (*SOCS1*, *RMI2*) (**Table 2**, **Supplementary Figure 3** and **Supplementary Data**).

Shared susceptibility with infection

The association between EBV with HL, coupled with epidemiological reports of HL also being associated with non-EBV infections[47-50], suggests shared susceptibility *a priori*. Support for such an assertion is provided by a recent report implicating a number of the HL loci, including 6q23.3, 16p11.2 and 20q13.12, as well as the HLA region, as determinants of risk of infection[42].

To investigate co-heritability between HL and susceptibility to infection, we implemented cross-trait LD score regression[41]. Using summary-level GWAS data, we estimated genetic correlations between HL and over 20 self-reported infections in 200,000 23andMe participants[42]. Overall no statistically significant correlation was shown between any specific infection and HL, NSHL or mixed cellularity Hodgkin lymphoma (**Supplementary Table 11**). Following on from this, for infections with greater than two genetically defined instrumental variables (IVs), we performed a Mendelian randomisation (MR) analysis to identify a potential causal relationship with HL. For tonsillectomy, yeast infections and childhood ear infections, no statistically significant associations were demonstrated (**Supplementary Tables 12**). A nominally significant positive association between self-reported mumps infection and HL was found (P = 0.04), however this was not significant after correction for multiple testing.

DISCUSSION

By utilising publicly available summary statistics we have increased the power of our study allowing us to identify five new HL risk loci, thus bringing the total number of HL risk loci to 18. Whilst our reliance on such data has restrained our ability to examine subtype-specific effects, it is likely that the newly described risk loci have generic effects on HL susceptibility as with the known risk loci at 5q31.1 and 19p13.3[12].

At the new and known HL risk loci, we observed an enrichment of active regulatory regions in germinal centre B-cells, CD4+ thymocytes, CD4+ T-cells and CD8+ T-cells. Furthermore, whilst some HL risk loci locate to H3K27Ac peaks in both B- and T-cells, a number display lineage-specificity. Motivated by this finding, we have utilised PCHi-C and gene expression data in these cell types to identify targets subject to regulatory control by HL risk SNPs. While in part speculative, and requiring functional validation, integrating proximity, cell specificity of risk loci, gene expression and PCHi-C data, our analyses highlight three biological processes and their associated genes as a basis of HL susceptibility (**Table 2**): the germinal centre reaction (2p16.1, *REL*[51]; 3q28, *BCL6* and *mir-28*[52,53]; 6p21, *HLA*[54]; 6q23.3, *MYB*[55]; 8q24.21, *MYC*[56]; 11q23.1, *POU2AF1*[57]; 16p11.2, *MAPK3*[58]; 19p13.3, *TCF3*[59]; 20q13.12, *CD40*)[60,61], T-cell differentiation and function (3p24.1, *EOMES*[62]; 5q31,1, *IL13*[63]; 6q22.33, *PTPRK* and *THEMIS*[64,65]; 6q23.3, *MYB*[66]; 6q23.3, *AHI1*[67]; 10p14, *GATA3*[68]; 16p13.1, *SOCS1* and *CLEC16A*[69,70]; 16p11.2, *MAPK3* and *CORO1A*[71,72]) and constitutive NF-κB activation (2p16.1, *REL*[73]; 3p24.1, *AZI2*[74]; 6q23.3, *TNFAIP3*[75]; 20q13.12, *CD40*[76,77]).

Our findings extend the relationship between germline genetics and tumor biology[45], as evidenced by enrichment of active chromatin marks for HL risk loci in L-428, and the finding of many of the target genes for HL GWAS associations are subject to somatic alterations in HRS cells, namely *REL*[78], *TNFAIP3* and *SOCS1*[79-81]. The composite cellular basis of the HL tumor represents a pre-eminent example of the importance of the cellular microenvironment for the development of cancer. Hence, it is entirely conceivable that some of the HL risk loci may impact on the development of the B-cell tumor indirectly. Support for such an assertion is the observation of T-cell specificity as well as the finding of an eQTL at 3p24.1 (*EOMES*) in CD8+ T-cells. Notably, Eomes^{Hi} T-bet^{Lo} PD-1^{Hi} CD8+ T-cells are considered to delineate a key subset of exhausted CD8+ T-cells[82,83] which may contribute to an immunosuppressive tumor microenvironment and is a feature of peripheral blood T-cells in HL[84].

There are a number of reasons for the observed lack of concordance between the PCHi-C and eQTL analysis at risk loci. Firstly, the resolution of the Hi-C library using *HindIII*, a 6-base pair cutter, is approximately 10kb. As such, we are unable to detect concordant chromatin contacts at risk loci which influence the expression of genes located <10kb. Secondly, it is recognised that the range at which gene expression is perturbed to influence disease risk, may be narrow and as such may not be detected by an eQTL analysis. Finally, given the risk loci are likely to act in specific cell populations, and our expression data is limited by broad B- and T-cell populations, it is possible that we have not captured the cell type to analyse expression. As such we would view both methods as complimentary in identifying target genes.

The established association between EBV and risk of HL, coupled with other epidemiological observations provides strong *a priori* evidence for infection being a major etiological risk factor for HL. While our MR analysis failed to implicate a causal relationship with any of the self-reported infection traits, we acknowledge that our study had limited power. It is, however, possible that pleiotropism between the 6p21.1, 6q23.3, 16p11.2 and 20q13.12 risk loci for HL and tonsillectomy is consistent with some form of a shared biological basis. This is intriguing since tonsillectomy has previously been linked to HL in some epidemiological observational studies[47].

In conclusion, our study provides further evidence for inherited susceptibility to HL and support for cell-type specificity at HL risk loci. Furthermore, through the integration of gene expression, histone modification and *in situ* PCHi-C data, our data highlights dysfunction of the germinal centre reaction, perturbed T-cell function and constitutive NF-κB activation as mechanisms by which genetic risk loci influence HL pathogenesis.

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DATA AVAILABILITY

Sequencing data, which forms the reference panel for imputation, have been deposited in the European Genome-phenome Archive (EGA) under accession codes EGAD00001000776.

Transcriptional profiling data from the MuTHER consortium that support the findings of this work have been deposited in the European Bioinformatics Institute (Part of the European Molecular Biology Laboratory, EMBL-EBI) under accession code E-TABM-1140.

ChIP-seq data from the Blueprint Epigenome Consortium are available from http://dcc.blueprint-epigenome.eu/#/home.

Hi-C data from the Blueprint Epigenome Consortium are available from https://osf.io/u8tzp/.

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Summary statistics for genetic susceptibility to infection-related traits are available upon request from 23andMe. Please visit research/23andme.com/collaborate to request access to these datasets.

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Table 1: Summary results for newly identified Hodgkin lymphoma risk loci. Freq, frequency; bp, base pair; OR, odds ratio; CI, confidence interval; I^2 proportion of the total variation due to heterogeneity.[¥] Summary statistics from 1,200 cHL patients and 6,417 controls[27]. †Genes at each risk locus are given for identification purposes only and does not necessarily indicate biological functionality.

		Risk		Discovery GWAS meta-analysis		UK Biobank		USC-IARC-UC-GWAS		Meta-analysis			
Locus	**Nearest genes†**	**allele (freq)**	**Position (hg19, bp)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	**I^2 (%)**	**P_{het}**
1p13.2, rs2476601	*PTPN22*	A (0.12)	114377568	3.92×10^{-3}	1.15 (1.04-1.26)	3.21×10^{-4}	1.42 (1.17-1.72)	3.70×10^{-3}	1.24 (1.07-1.44)[¥]	4.20×10^{-7}	1.21 (1.12-1.30)	20	0.29
6p21.31, rs649775	*ITPR3- UQCC2-IP6K3*	A (0.11)	33684313	4.00×10^{-6}	1.25 (1.14-1.38)	-	-	8.22×10^{-6}	1.36 (1.19-1.55)	2.11×10^{-10}	1.29 (1.19-1.40)	0	0.54
6q23.3, rs1002658	*OLIG3-TNFAIP3*	T (0.18)	137981584	3.86×10^{-6}	1.19 (1.11-1.28)	-	-	2.15×10^{-3}	1.18 (1.06-1.31)	2.97×10^{-8}	1.19 (1.12-1.26)	0	0.53
11q23.1, rs7111520	*POU2AF1*	A (0.70)	111249611	4.33×10^{-7}	1.17 (1.10-1.24)	-	-	4.39×10^{-6}	1.24 (1.13-1.35)	1.44×10^{-11}	1.19 (1.13-1.25)	0	0.68
16p11.2, rs6565176	*MAPK3-CORO1A*	T (0.48)	30174926	8.64×10^{-6}	1.14 (1.08-1.21)	3.44×10^{-4}	1.28 (1.10-1.23)	-	-	4.00×10^{-8}	1.16 (1.10-1.22)	0	0.46
20q13.12, rs2425752	*NCOA5-CD40*	T (0.23)	44702120	2.23×10^{-4}	1.13 (1.06-1.20)	2.94×10^{-4}	1.30 (1.12-1.50)	3.77×10^{-3}	1.14 (1.09-1.20)	2.01×10^{-8}	1.15 (1.10-1.21)	56	0.06

Table 2: Integration of expression quantitative trait loci, histone modification, promoter capture Hi-C data at non-HLA Hodgkin lymphoma risk loci to identify candidate causal genes at Hodgkin lymphoma risk loci. bp, base pair; cHL, classical Hodgkin lymphoma; NSHL; nodular sclerosis Hodgkin lymphoma; SNP, single nucleotide polymorphism; LCL, lymphoblastoid cell lines; LD, linkage disequilibrium. ¥SNPs (r^2 < 2.5 kilobases from ChIP-seq peak).

Locus	Sentinel SNP	Position (bp, hg19)	Gene(s) in LD block	Coding variant(s)	Promotor /UTR variant(s)	Expression quantitative trait loci in LCL	Expression quantitative trait loci in T-cell	H3K27Ac histone peak¥	Hi-C contact(s) in naïve or total B-cells	Hi-C contact(s) in T-cells	Hi-C contact(s) in HRS cell	Evidence of perturbation in HL	Candidate biological mechanism
2p16.1	rs2420518	61054980						Naïve B-cell	*REL*	*REL*		*REL*[85]	Constitutive NF-κB activation (*REL*)[73] Altered B-cell differentiation and germinal centre reaction (*REL*)[51]
3p24.1	rs3806624	27764623	*EOMES*		*EOMES* (3'-UTR)		*EOMES* (↑) (CD8+)	Effector memory CD8+ T-cell Plasma cell L-428	*AZI2*, *CMC1*, *NEK10*, *OXSM*, *NGLY1*, *ZCWPW2*	*EOMES*, *AZI2*, *CMC1*, *NEK10*, *OXSM*, *NGLY1*, *ZCWPW2*	*AZI2* *CMC1*	*EOMES*[86]	Exhausted CD8 T-cell phenotype (*EOMES*)[62,82,83] Constitutive NF-κB activation (*AZI2*)[74]
3q28	rs4459895	187954414	*LPP*					CD38- naïve B-cell Naïve B-cell Germinal centre B-cell L-428				*BCL6*[87]	Dysfunction of B-cell germinal centre reaction (*BCL6*, *mir-28*)[52,53]
5q31.1	rs848	131996500	*IL-13*	(p.Gln144Arg)	*IL-13* (3'-UTR)			L-428				*IL-13*[88]	Altered CD4+ T-cell function (*IL-13*)[63]
6p21.31	rs649775	33684313	*ITPR3* *UQCC2* *IP6K3*		IP6K3 (3'-UTR)	*ITPR3* (↓)		CD4+ T-cell CD8+ T-cell Effector memory CD8+ T-cell Naïve B-cell Class switched memory B-cell	*BAK1*, *SYNGAP1*, *GGNBP1*, *LINC00336*	*BAK1*, *GRM4*, *SYNGAP1*, *KIFC1*, *CUTA*, *PHF1*, *GGNBP1*, *LINC003336*			Altered B-cell differentiation (*ITPR3*)[89]
6q22.33	rs9482849	128288536	*PTPRK*					CD4+ T-cell Central memory CD4+ T-cell CD8+ T-cell Effector memory CD8+ T-cell L-428	*PTPRK* *THEMIS*			*PTPRK*[90]	Altered T-cell differentiation (*PTPRK*, *THEMIS*)[64,65]
6q23.3	rs9402684	135419305	*HBS1L*					CD3- CD4+ CD8+ thymocyte CD3+ CD4+ CD8+ thymocyte CD4+ T-cell Central memory CD4+ T-cell CD8+ T-cell Effector memory CD8+ T-cell Germinal centre B-cell Plasma cell L-428	*MYB*		*MYB*		Altered T-cell differentiation (*MYB*)[66,91] Altered B-cell differentiation and germinal centre reaction (*MYB*)[55]
6q23.3	rs6928977	135626348	*AHI1*			*AHI1* (↑) *ALDH8A1* (↑)	*AHI1* (CD4+ and CD8+) (↑)	CD3+ CD4+ CD8+ thymocyte					Altered T-cell differentiation (*AHI1*)[67]
6q23.3	rs1002658	137981584						L-428	RP11-204P2.3		TNFAIP3	TNFAIP3[79]	Constitutive NF-κB activation (*TNFAIP3*)[75]
8q24.21	rs34748721	129195943						Naïve B-cell Class switched memory B-cell	*CASC11, MYC, PVT1, RNU1-106P, MIR1207*			*MYC*[92]	Dysfunction of B-cell germinal centre reaction (*MYC*)[56,77]
10p14	rs2388486	8099021	*GATA3*			*GATA3*(↓)		CD3- CD4+ CD8+ thymocyte CD3+ CD4+ CD8+ thymocyte CD4+ T-cell CD8+ T-cell				*GATA3*[93]	Altered T-cell differentiation (*GATA3*)[68]

								Effector memory CD8+ T-cell Germinal centre B-cell					
10p14	rs3781093	8101927	*GATA3*			*GATA3* (↓)		CD4+ T-cell CD8+ T-cell				*GATA3*	Altered CD4+ T-cell differentiation (*GATA3*)[68] Altered B-cell differentiation (*GATA3*)[94]
11q23.1	rs7111520	111249611	*POU2AF1*			*COLCA1* (↑) *COLCA2* (↑)		CD4+ T-cell Central memory CD4+ T-cell CD8+ T-cell CD38- B-cell CD38- naïve B-cell Naïve B-cell Germinal centre B-cell Unswitched memory B-cell Class switched memory B-cell Plasma cell	FDX1	FDX1, PPP3R1B, ALG9, FDXACB1, DIXDC1		*POU2AF1*[95]	Dysfunctional germinal centre reaction (*POU2AF1*)[57]
13q34	rs112998813	115059729	*UPF3A*			*CDC16* (↑) *UPF3A* (↓)	*CDC16* (CD4+ and CD8+) ↑)	CD4+ T-cell Central memory CD4+ T-cell CD8+ T-cell Effector memory CD8+ T-cell CD38- naïve B-cell Naïve B-cell Germinal centre B-cell Unswitched memory B-cell Class switched memory B-cell Plasma cell		*RASA3*, *TMEM255B*, *GASA6*		*CDC16*[86]	Disrupted cell cycle regulation (*CDC16*)[96] Dysfunction of mRNA surveillance (*UPF3A*)[97]
16p13.13	rs34972832	11198938	*CLEC16A*			*SOCS1* (↑)		CD4+ T-cell Central memory CD4+ T-cell CD8+ T-cell Effector memory CD8+ T-cell Naïve B-cell Germinal centre B-cell Class switched memory B-cell Plasma cell L-424	*RMI2*	*SOCS1,* *RMI2*, *PRM2*, *PRM3*, *TNP2*, *HNRNPCP4*	*SOCS1* *RMI2*	*SOCS1*[81]	T-cell dysfunction (*SOCS1*)[69]. Altered T-cell differentiation (*CLEC16A*)[70] B-cell dysfunction (*CLEC16A*)[98] Genomic instability (*RMI2*)[99]
16p11.2	rs6565176	30174926	*CORO1A*		*CORO1A* (5'-UTR)	*MAPK3* (↓) *BOLA2* (↓)		CD4+ T-cell CD8+ T-cell Effector memory CD8+ T-cell Naïve B-cell Class switched memory B-cell				*MAPK3*[100] *CORO1A*[101]	T-cell dysfunction (*CORO1A* and *MAPK3*)[64,71,72] Dysfunction of B-cell germinal centre reaction (*MAPK3*)[58,102,103]
19p13.3	rs2012125	1630341	*TCF3A*					CD38- B-cell Naïve B-cell Class switched memory B-cell					Dysfunction of B-cell germinal centre reaction (*TCF3A*)[104]
20q13.12	rs2425752	44702120	*NCOA5* *CD40*			CD40 (↓) WFDC10B (↑)		Central memory CD4+ T-cell CD8+ T-cell Effector memory CD8+ T-cell Naïve B-cell Germinal centre B-cell L-428	CD40	TP53RK		*CD40*[105]	Dysfunctional germinal centre reaction (*CD40*)[54,61] Constitutive NF-κB activation (*CD40*)[76,77]

FIGURES

Figure 1: Genome-wide meta-analysis *P* values of Hodgkin's lymphoma risk ($-\log_{10}P$, *y* axis) plotted against their chromosomal positions (*x* axis). Novel HL risk loci and candidate gene are in orange.

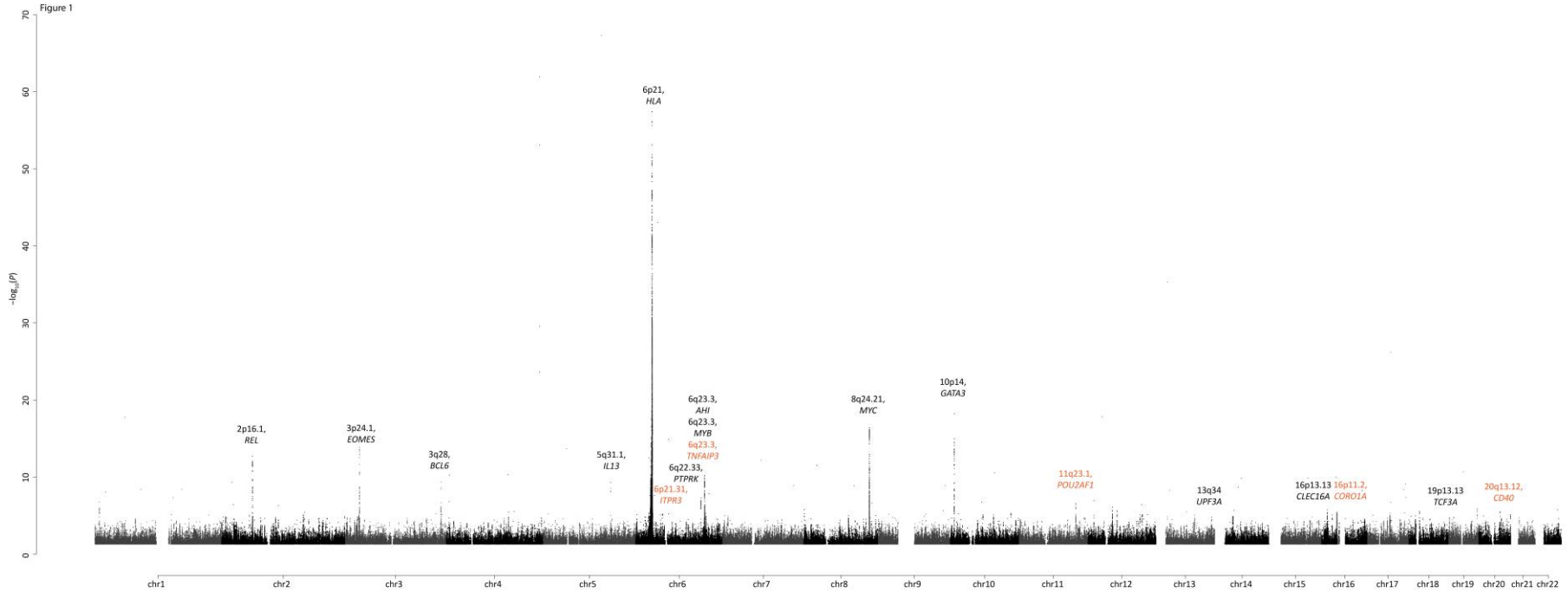
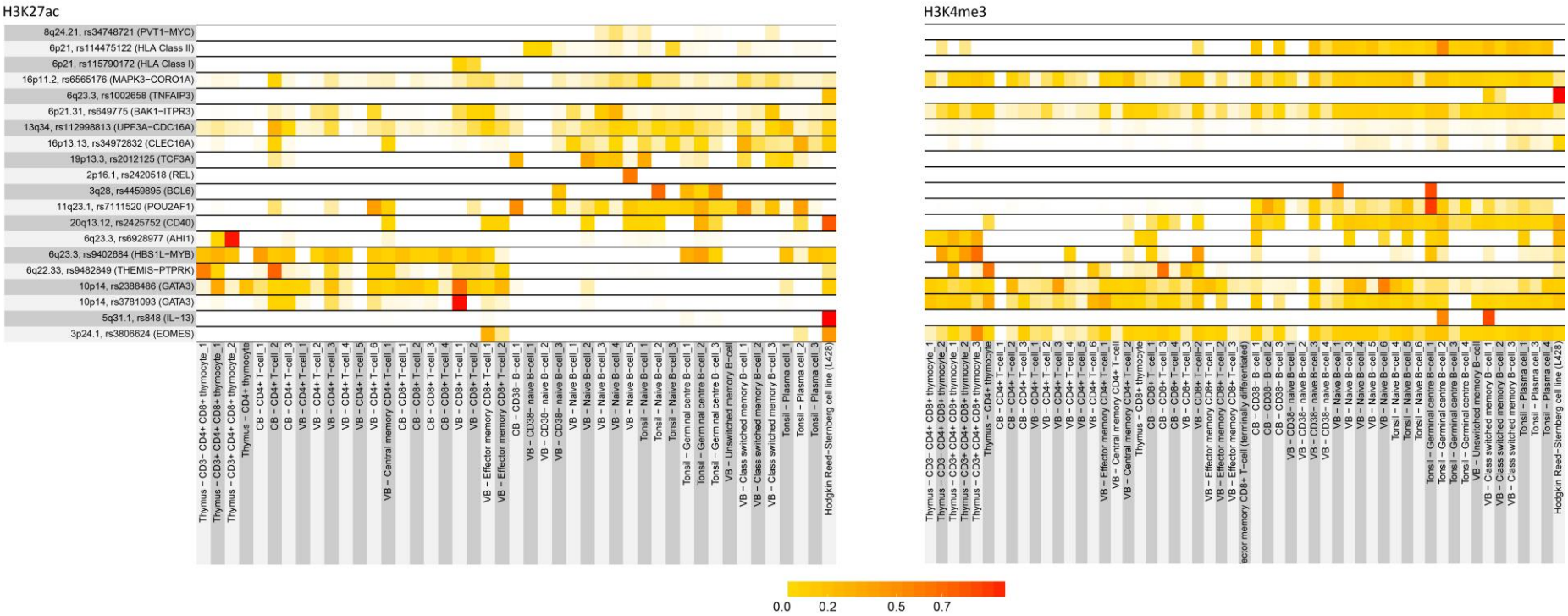


Figure 2: Heat map of SNP scores for H3K27Ac and H3K4me3 at each Hodgkin lymphoma risk locus. SNP score calculated as *per* Trynka *et al.*[30] For each SNP at a given locus, the score represents the height of the closest ChIP-seq peak divided by the distance to the summit in each each cell line, normalised across all immune cell types. Thus, a SNP within a chromatin mark that is active in only one cell type will have a high score of 1 (red) in that cell type and 0 (white) in others. In contrast, a SNP close to chromatin marks that are not cell type specific will have similarly modest scores across cell types. Genes at each risk locus are given for identification purposes only and do not necessarily indicate biological functionality.

Figure 2


H3K27ac
8q24.21, rs34748721 (PVT1−MYC)
6p21, rs114475122 (HLA Class II)
6p21, rs115790172 (HLA Class I)
16p11.2, rs6565176 (MAPK3−CORO1A)
6q23.3, rs1002658 (TNFAIP3)
6p21.31, rs649775 (BAK1−ITPR3)
13q34, rs112998813 (UPF3A−CDC16A)
16p13.13, rs34972832 (CLEC16A)
19p13.3, rs2012125 (TCF3A)
2p16.1, rs2420518 (REL)
3q28, rs4459895 (BCL6)
11q23.1, rs7111520 (POU2AF1)
20q13.12, rs2425752 (CD40)
6q23.3, rs6928977 (AHI1)
6q23.3, rs9402684 (HBS1L−MYB)
6q22.33, rs9482849 (THEMIS−PTPRK)
10p14, rs2388486 (GATA3)
10p14, rs3781093 (GATA3)
5q31.1, rs848 (IL−13)
3p24.1, rs3806624 (EOMES)
Thymus − CD3− CD4+ CD8+ thymocyte_1
Thymus − CD3+ CD4+ CD8+ thymocyte_1
Thymus − CD3+ CD4+ CD8+ thymocyte_2
Thymus − CD4+ thymocyte
CB − CD4+ T−cell_1
CB − CD4+ T−cell_2
CB − CD4+ T−cell_3
VB − CD4+ T−cell_1
VB − CD4+ T−cell_2
VB − CD4+ T−cell_3
VB − CD4+ T−cell_4
VB − CD4+ T−cell_5
VB − CD4+ T−cell_6
VB − Central memory CD4+ T−cell_1
CB − CD8+ T−cell_1
CB − CD8+ T−cell_2
CB − CD8+ T−cell_3
CB − CD8+ T−cell_4
VB − CD8+ T−cell_1
VB − CD8+ T−cell_2
VB − Effector memory CD8+ T−cell_1
VB − Effector memory CD8+ T−cell_2
CB − CD38− B−cell_1
VB − CD38− naive B−cell_1
VB − CD38− naive B−cell_2
VB − CD38− naive B−cell_3
VB − Naive B−cell_1
VB − Naive B−cell_2
VB − Naive B−cell_3
VB − Naive B−cell_4
VB − Naive B−cell_5
Tonsil − Naive B−cell_1
Tonsil − Naive B−cell_2
Tonsil − Naive B−cell_3
Tonsil − Germinal centre B−cell_1
Tonsil − Germinal centre B−cell_2
Tonsil − Germinal centre B−cell_3
VB − Unswitched memory B−cell
VB − Class switched memory B−cell_1
VB − Class switched memory B−cell_2
VB − Class switched memory B−cell_3
Tonsil − Plasma cell_1
Tonsil − Plasma cell_2
Tonsil − Plasma cell_3
Hodgkin Reed−Sternberg cell line (L428)
H3K4me3
Thymus − CD3− CD4+ CD8+ thymocyte_1
Thymus − CD3− CD4+ CD8+ thymocyte_2
Thymus − CD3+ CD4+ CD8+ thymocyte_1
Thymus − CD3+ CD4+ CD8+ thymocyte_2
Thymus − CD3+ CD4+ CD8+ thymocyte_3
Thymus − CD4+ thymocyte
CB − CD4+ T−cell_1
CB − CD4+ T−cell_2
CB − CD4+ T−cell_3
VB − CD4+ T−cell_1
VB − CD4+ T−cell_2
VB − CD4+ T−cell_3
VB − CD4+ T−cell_4
VB − CD4+ T−cell_5
VB − CD4+ T−cell_6
VB − Effector memory CD4+ T−cell_1
VB − Central memory CD4+ T−cell_1
VB − Central memory CD4+ T−cell_2
Thymus − CD8+ thymocyte
CB − CD8+ T−cell_1
CB − CD8+ T−cell_3
CB − CD8+ T−cell_4
VB − CD8+ T−cell_3
VB − Effector memory CD8+ T−cell−2
VB − Effector memory CD8+ T−cell_1
VB − Effector memory CD8+ T−cell_2
VB − Effector memory CD8+ T−cell_3
ector memory CD8+ T−cell (terminally differentiated)
CB − CD38− B−cell_1
CB − CD38− B−cell_2
CB − CD38− B−cell_3
VB − CD38− naive B−cell_1
VB − CD38− naive B−cell_2
VB − CD38− naive B−cell_3
VB − CD38− naive B−cell_4
VB − Naive B−cell_1
VB − Naive B−cell_3
VB − Naive B−cell_4
VB − Naive B−cell_5
VB − Naive B−cell_6
Tonsil − Naive B−cell_4
Tonsil − Naive B−cell_5
Tonsil − Naive B−cell_6
Tonsil − Germinal centre B−cell_1
Tonsil − Germinal centre B−cell_2
Tonsil − Germinal centre B−cell_3
Tonsil − Germinal centre B−cell_4
VB − Unswitched memory B−cell
VB − Class switched memory B−cell_1
VB − Class switched memory B−cell_2
VB − Class switched memory B−cell_3
Tonsil − Plasma cell_1
Tonsil − Plasma cell_3
Tonsil − Plasma cell_4
Hodgkin Reed−Sternberg cell line (L428)
0.0
0.2
0.5
0.7